

The Penicillin Treatment of Scarlet Fever

Inaugural-Dissertation

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von

Murray Arnold

New York, N. Y., U. S. A. 1958. Basel, Schweiz

BASEL - BUCHDRUCKEREI GUSTAV HÜGIN - 1958

Aus dem Kinderspital Basel, Direktor: Prof. Dr. A. Hottinger.
(Arbeit unter Leitung von PD. Dr. F. Hauser)

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Professor Dr. med. *A. Hottinger*.

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Introduction and History

Scarlet fever is an acute infectious disease or rather a syndrome, caused by haemolytic streptococci group A, characterized by Enanthema-Exanthema, acute upper respiratory inflammation, desquamation, and, after a certain symptomfree interval, followed by a characteristic group of complications, varied and multifaceted, the so-called "zweites Kranksein".

Sydenham described the disease and coined the term Scarlet Fever in 1675, but for at least 50 years earlier, it had been recognized as a clinical entity associated with serious late complications. The streptococcal etiology of the disease was suggested by many investigators in the late 19th and early 20th century, and was fully established by the early 20th century. Löffler, in 1884, was the first to identify the streptococcus in a throat culture. Schottmüller standardized the procedure of cultivating the streptococcus when he discovered the blood agar culture medium in 1895. The various substances produced by streptococci, and, which probably play a role in the disease process, have been described and studied by the Dicks, Tillet and Dochez.

Earlier workers believed that scarlet fever was caused by a single strain of streptococcus. It is now clear that many different serologic types of these organisms are capable of producing the disease. On the basis of culture reactions, when grown on an agar plate, it is possible, when the plate contains blood, to divide the streptococci into 3 fundamental classes. The alpha colonies show a zone of incomplete lysis and greening or methaemoglobin formation in the red blood corpuscles in the medium surrounding the colony; beta streptococci exhibit a clear zone of complete haemolysis, and finally, gamma streptococci exhibit no reaction.

Although knowledge of the reactions of streptococci on blood agar plates is useful as an indication of the possible pathogenicity of the organism, it was not until the work of Griffith and Lancefield, devising a serologic classification, that the epidemiologic and immun-

ologic features of streptococcal infections were established. A polysaccharide termed "c Substance" is present in the streptococcus cell and reacts in a precipitation test with a specific antiserum. On the basis of this reaction, it has been possible to divide streptococci into 12 groups: A, B, C, D, E, F, G, H, K, L, M and N.

Numerous investigations have shown that most respiratory infections and scarlet fever in man are caused by Lancefield's group A streptococci. Originally it was thought that the Lancefield groups included only the beta streptococci. It is now known that there are some alpha and gamma streptococci in most of the groups.

Not only may streptococci be classified by grouping, but also most groups contain several different types. Group A, of primary interest to the clinician, comprises at least 40 specific types. Typing is based either on an agglutinin reaction by the Griffith technic or on the precipitation test as described by Swift, Wilson and Lancefield. The type specific substance is the T substance in the former method, and the M substance in the latter method. Extensive study has shown the M substance to be a protein.

The terminology used to classify streptococcal infections of the upper respiratory tract had been in use for many years prior to the time it was realised that septic sore throat, acute tonsillitis and pharyngitis were all caused by the numerous types of group A streptococci. This was an important observation and in many countries scarlet fever is considered the same as acute tonsillitis or pharyngitis, with the exception that many types of group A streptococci produce erythrogenic toxin. Acute tonsillitis caused by one of these toxin producing types of group A streptococci, in a person without circulating antibodies may be associated with an exanthema, and the disease is then called scarlet fever. If a person has adequate antitoxin to neutralize the toxin produced by the bacteria, there would result an acute tonsillitis or scarlatina sine exanthemata.

This manifold etiology of scarlet fever and streptococcal infections in general is important to understand for our later discussion, as it explains partly the wide variability of complications and the changing clinical picture of scarlet fever, and also the problem of reinfection. The Scandinavian pediatrician Lichtenstein, by careful cultivation of the throat swabs of scarlet fever patients, was able to correlate the severity of the clinical picture with the streptococcus

type. In mild cases, type 1 and 2 were most frequent, while in severe cases type 3 and 4 were predominant. Also in various epidemics, the relationship of the streptococcus type and the complications caused, has been investigated. Rammelkamp and his associates in the United States Army saw a relationship between type 12 and glomerulonephritis as a complication. All the Griffith streptococcus types can build the erythrogenic toxin, although this varies in intensity with the different types.

In addition to the erythrogenic toxin built by the group A, other antigenes are produced like streptolysin O, streptolysin S and fibrinolysin.

The epidemiology of scarlet fever has also been studied. Before World War II, the Rockefeller Institute sent to Rumania a group under Schwentker, Janney and Gordon who studied the spread of this disease in the community, its relation to streptococcus type and the relation of healthy carriers and atypical cases to the development of immunity.

The immunization of scarlet fever has been studied especially by the Dicks.

Immunity to scarlet fever is both antibacterial and antitoxic. The antitoxic part is the most important for scarlet fever, as it is permanent and as it protects against the rash. The antibacterial immunity is type specific and explains the frequent repetition of tonsillitis and pharyngitis and the possibility of superinfection and scarlatina sine exanthemata by different types of group A streptococci.

As our knowledge of the etiology, immunology and epidemiology grew, there was also a gradual evolution in the therapeutics of scarlet fever. Before the epoch making announcement of Domagk in 1935, that Prontosil was a specific antibacterial agent for haemolytic streptococci, only antitoxin was available in the treatment of scarlet fever. In the serum therapy of scarlet fever, horse serum is used, but in the presence of an allergy, human reconvalescent serum is preferable. In the many years of its use, much literature has accumulated over its usefulness. The Dicks were very enthusiastic, and in many articles spread over the years 1924 to 1932 reported favourable results with antitoxin against the initial toxic symptoms, especially the exanthema. In addition, the Dicks reported in a large series of cases, comparing many hundreds of cases only handled

symptomatically with cases treated with antitoxin, a decrease in the suppurative complications like otitis media as well as the late toxic-allergic complications like myocarditis and nephritis. Banks, in 1933, in England, reported a drop in complications from 33 % to 9,5 % with intravenous streptococcus horse serum. However, with these favourable results, many serious serum reactions also came, which in one case led to death.

In 1949, in America, F. Silver, for the first time introduced gamma globulin for the treatment of scarlet fever. In a series of 207 patients he treated 83 with gamma globulin, 74 with antitoxin and 50 patients only symptomatically as a control group. He was very enthusiastic with gamma globulin and reported a decrease in the duration of the exanthema, a reduction of the fever, and a reduction of the complications to 15,7 % as compared to the 24 % of the control group. The next year (1950), Weinstein, also in America, discouraged the use of gamma globulin in a series of articles.

In addition to the use of antitoxin and gamma globulin prophylactic vaccination was also introduced in the 1920's to be used for Dick positive persons. The vaccination was enthusiastically endorsed by the Dicks, who said that the immunity lasted approximately 12 years. MacRaye and Watson developed the vaccination material and concentrated it, and reported transformation of Dick positive to Dick negative in 100 % of the cases, and also a complete protection against the disease. The vaccination was enthusiastically received in America. Anderson (1938) made a control study of the vaccination program with nurses in a hospital. In a series of 747 nurses, he vaccinated 298 of them and none of these contracted scarlet fever. In the remaining 449 nurses, there were 15 cases of the disease. In Europe the reception to the vaccination program was the opposite. Lorenz and Haidvogel were completely disappointed. Between 1948 and 1950, in Germany, they compared scarlet fever cases in vaccinated and non-vaccinated patients and observed no improvement with vaccination.

About the year 1943 sulfonamide was introduced for the treatment of scarlet fever. In Switzerland, Wolfensberger in Zurich (1943), was the first to compare control patients with patients treated with sulfonamide. Fox and Gordon (1944) in America, in a control series of 1000 cases, advised sulfonamide for scarlet fever.

The results from other clinics were contradictory with favourable results from German clinicians like Schmeiser (1952) and Blittersdorf (Eleudron) and unfavourable reports from the Italian authors Rappellini and Di Nola from the Torino medical clinic.

After the war, with the release of penicillin, the treatment with sulfonamide was quickly abandoned. As penicillin was available in America sooner than in the other countries, the first reports of the treatment of scarlet fever with penicillin came from there. The first reports were from the Boston City Hospital and the United States Navy. The dosage used in these early days were small compared to 1957 standards. The average dose was 10 000 U. every 3 hours with an additional local treatment by spray. Meads (1945), Ashley (1946).

In December 1945, penicillin came to the continent and Jersild, in Copenhagen, was the first to use it. On the following years, the use of penicillin for the treatment of scarlet fever, as well as all other infectious diseases, spread rapidly. In Basel it was first introduced in 1947 and began to be used intensively in the 1948 Basel scarlet fever epidemic. With the introduction of penicillin, there were soon published comparisons between the penicillin treatment and symptomatic treatment. Many comparisons between penicillin and sulfonamide were also made. In America, Hoyne and Brown, Hirsh, Dowling and Sweet, commented favourably. In Europe, Jersild in Copenhagen, and Hedland in Sweden, published favourable reports. It is not appropriate to comment in detail on these reports now. In our later discussion we will refer to them. The dosage of penicillin was gradually raised throughout the world. At first it was usually given locally as a throat spray. This was soon abandoned, as it proved useless. The intragluteal injection of crystallin penicillin was popular for years and the dosage was gradually increased: 100 000 U. daily to 200 000 U., to 300 000 U. and then, when older children or adults were involved, to 600 000 U. daily for 6 days. Since this necessitated injections 4 times a day, attempts were made to manufacture preparations that could be delayed. This led to the introduction of depot preparations and procaine penicillin. The end result is bicillin intramuscular, which can be injected only once and suffice for the entire treatment.

With very toxic patients combination treatment of penicillin and

antitoxin, penicillin and gamma globulin or penicillin and convalescent serum was used, the logic being that penicillin influences the bacterial component of scarlet fever while the antibody influences specifically the toxic component — the combination being synergistic.

In addition, the broad spectrum antibiotics were used. Aureomycin, erythromycin and terramycin were introduced with favourable results.

Many clinical reports were made during the years between 1946 and 1956. Many came from America — Weinstein, Rantz, Hoyne, Ashley, Rammelkamp. Many came from Germany — Mayer, Kraft, Herrlich, Ebert, Hoen, Schmeiser, Linios, Maué, Ströder and Wiesner. Many came from the Scandinavian lands — Jersild, Ström, Ancheron, Hedlund, Lichtenstein, and from Switzerland — Hottinger, Pulver, Glanzmann, Gautier, Thélín, Freudenberg, Grasset. Many results were favourable, others were not.

Penicillin created wonders and caused problems.

Methods and Material

In the next few pages we will discuss some observations on the clinical material of the Basel Children's Hospital. We have observed in Basel 2332 cases that were entered in our Hospital for scarlet fever. We have observed the effect of penicillin on the 1) initial fever, 2) exanthema, 3) complications both septic and toxic, and 4) hospitalization. We have also observed some problems that have arisen with the evolution of the penicillin therapy.

In the Basel Children's Hospital, the annual number of hospitalized patients with scarlet fever has decreased gradually during the last 10 years, the apparent reason being that more cases are handled at home by the family physician. The treatment of scarlet fever has been so simplified that hospitalization is often not necessary.

On reappraisal of these cases, all cases were eliminated which were only suspected scarlet fever, without certain diagnosis. Also eliminated were those cases where clinical signs of the disease had ended and which were being treated merely as streptococcus carriers.

Table I

Year	Number	Males	Females
1947	272	133	139
1948	334	160	174
1949	410	200	210
1950	344	153	191
1951	201	102	99
1952	154	68	86
1953	170	78	92
1954	158	70	88
1955	176	93	83
1956	113	47	66
Total 10	2332	1104	1228

Total Patients in Hospital

Our final observation material that was included in our statistics is listed below.

Table II

Year	Number	Males	Females
1947	272	133	139
1948	310	151	159
1949	405	195	210
1950	344	153	191
1951	193	102	91
1952	154	68	86
1953	161	78	83
1954	158	70	88
1955	176	93	83
1956	113	47	66
Total 10	2286	1090	1196

Case Material analysed

One can observe a gradual rise in the number of cases from 1947 to 1948, which was an epidemic year in Basel; a peak reached in 1949 with over 400 cases, and then a gradual decline through the

ensuing years to reach a minimum in 1956 with only 113 cases, a decline of nearly 300 % from 1949.

Our 2286 patients had received various treatment for scarlet fever through the years paralleling the evolution in the treatment in these years in the rest of the world. In Basel the same gradual evolution had taken place. Thus the patients treated during 1947 and early 1948, and several cases in 1949 were largely treated symptomatically. Some received sulfonamide preparations like elkodin, others received serum treatment. Penicillin treatment for scarlet fever was introduced in Basel in 1947, and the dosage was gradually increased through the following years.

According to their treatment, our original 2286 patients were grouped in 3 large categories. Thus the patients in the years 1947, 1948 and several in 1949, that had received no penicillin, were grouped together in a group that will henceforth be referred to as group I. Whether they had received sulfonamide, serum or just symptomatic treatment, they had all in common that they had not received penicillin. This group comprised 420 patients.

At first penicillin dosage for scarlet fever in Basel was, according to 1957 standards, relatively small. At first the penicillin was applied locally on the throat in the form of a spray. 6 000 U. daily intramuscularly were tried in several cases in 1947. These patients formed the beginning of our group II, and in this group were included all patients in 1948, in the epidemic year, who had received penicillin, and all patients in the years 1949, 1950, 1951, 1952 and 1953 who had received penicillin. If during these years a patient received no penicillin, he was placed in group I. If he received another antibiotic like aureomycin in addition to or instead of penicillin, he was still placed in group II. During these years, the dosage of penicillin was increased from 6 000 U. daily to 300 000 U. daily for 5 to 6 days, and various preparations were used like crystalline penicillin and the depot preparations like dibenzylethylenediamine.

Our last group comprises the patients of the years 1954, 1955 and 1956, when the dosage of penicillin reached its maximum with an average of 600 000 U. daily for 5 days or less, depending on the severity of the case. This last group will henceforth be referred to as group III. Our final figures were:

Table III

Group I	Group II	Group III
420	1419	447
no penicillin	moderate penicillin	maximum penicillin

Division according to Therapy

An analysis of the severity of the cases was made in each of the groups to determine the legitimacy of a comparison. Each group was classified into 3 degrees of severity; mild scarlet fever, moderate or severe. This was made on the basis of presenting symptoms like fever, toxicity, pharyngitis and initial angina. The cases in which the fever did not exceed $38,5^{\circ}$ were considered mild, while those cases, in which the fever was between $38,5$ and 40° were considered moderate. Finally those with fever over 40° were included in our severe cases. It was also important to see if the severity of scarlet fever had changed during the last 10 years. Had the severity declined? During the last century (Hottinger) scarlet fever was a dreaded disease with a high mortality. In the 20th century it has lost most of its danger, and to be sure, this had occurred before 1947 and the discovery of penicillin. Had this decline reduced the severity of the cases in 1956 under those of 1947? The explanation of this decline is not too well understood. A change in the "genius epidemicus" or a change in the immunity reaction of the population has been indicated. Banks, in England, writes about the mildness of scarlet fever in Western Europe in the last 50 years and indicated a change in the streptococcus type as the main cause.

In our case material throughout the 10 years a preponderant number of cases were of the mild type. In group I mild cases comprised 70,3 % of the total, while in group II 68 % and in group III 67,5 % were mild cases. Similarity was also noted, as indicated in table IV, in the number of moderate cases. So, while it is undoubtedly true that even before penicillin therapy, scarlet fever had lost most of its dread, it was considered legitimate to make a comparison. Incidentally the number of severe cases of scarlet fever as minimal and

during the last 4 years in Basel, 4 deaths have been attributed to the acute severe form.

Table IV

	Group I	Group II	Group III
mild	70,3 %	68,0 %	67,5 %
moderate	28,4 %	29,5 %	31,5 %
severe	1,3 %	2,5 %	1,0 %
Total	100,0 %	100,0 %	100,0 %

Division according to Severity

It was our purpose to see the effect of increased dosage of penicillin on scarlet fever and also the effect of the time element, that is, the variation of the efficiency of penicillin in relation to the day of the illness when treatment was begun. Accordingly, our groups II and III, which had received penicillin, were further regrouped into 3 new subgroups, according to the day on which they had been treated. The group of patients treated the first or second day, was called group X. Patients who received treatment during the third or fourth day, were placed in group Y, while when treatment was begun after the fourth day, group Z received the patients. Sometimes it was difficult to be more accurate, as many patients were first given their penicillin by the family physician and afterwards admitted to the hospital. This caused problems, because it was not known exactly, how much penicillin the house doctor had given. In such a case it was assumed to be the usual dosage for the particular year.

We found that in group III more patients, 45 %, had received penicillin during the first two illness days than group II, where this subgroup was only 41 %. As later discussion will show, this is a favourable trend. Also in group III there were less patients receiving penicillin after the fourth day than in group II; also a favourable tendency.

Division according to Beginning of Therapy

Table V

	1 st & 2 nd day	3 rd & 4 th day	5 th day & over	total
Group II	583	723	113	1419
Group III	205	211	31	447

Table VI

	1 st & 2 nd day	3 rd & 4 th day	5 th day & over	total
Group II	41,0 %	51,0 %	8,0 %	100 %
Group III	45,0 %	48,0 %	7,0 %	100 %

Analysis of Fever

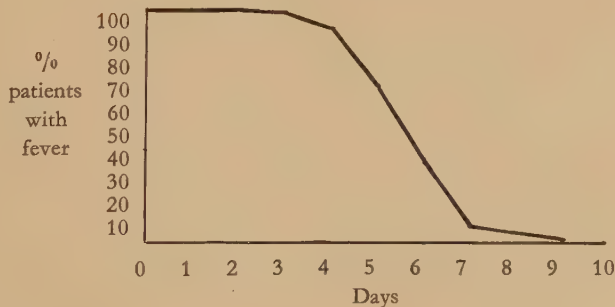
Our first comparison of groups I, II and III was in relation to the initial fever, and its disappearance under the treatment with penicillin, in respect to time and dosage.

Table VII

Group I

Average Fever Duration
= 5,85 Days

No. of patients	Fever days
6	9,0
2	8,5
12	8,0
14	7,5
74	7,0
42	6,5
90	6,0
40	5,0
68	5,5
35	4,5
32	4,0
2	3,5
3	3,0
0	2,5



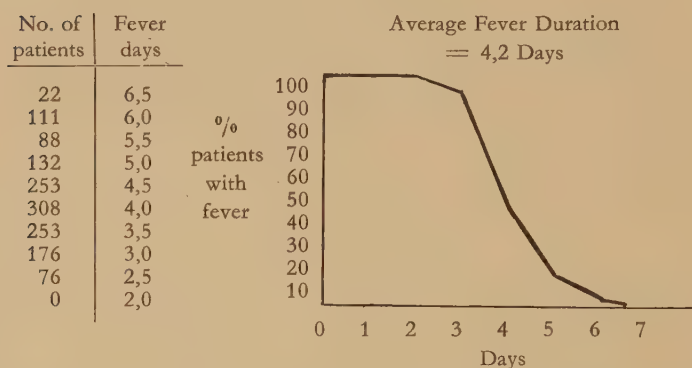
Below in table VII is the analysis of group I, our group that had received no penicillin.

We see that the average duration of fever is 5.85 days, calculated from the first day of the illness. No patient is feverless before the third day, and a small number of patients remain with fever until the 10th day.

In group II, under the influence of penicillin, the fever duration is significantly reduced and the average is 4.2 days. This is graphically depicted in table VIII below.

Table VIII

Group II



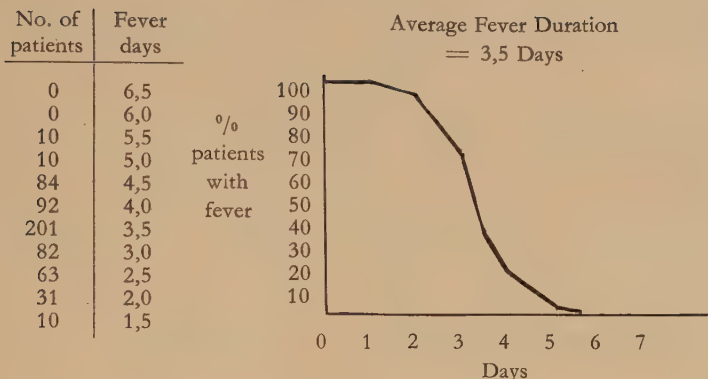
Patients started to become feverless by the third day and by the seventh day no patient had a fever, in contrast to group I, where many patients had fever through the 7th, 8th and 9th day.

Also, we noted that the patients of group II, who had received penicillin the first two days of the illness, had an average fever duration of 3.5 days, which is less than the average of the entire group II. The patients in group II x, who had received penicillin still later, had on the average the longest fever periods. In table IX is shown an analysis of group II x.

The importance of the last graph is obvious, because it shows how important it is to begin the treatment early. The influence of penicillin on scarlet fever is twofold. The fever in scarlet fever has a double origin. The bacterial infection of the streptococcus is a source of inflammation, and the toxin produced by the bacteria also causes

Table IX

Group II x



inflammation; the fever being a reaction to this inflammation. It is probably more the bacterial component that penicillin influences rather than the toxic component, although, as later shown, the drug also influences the exanthema, a purely toxic symptom. This would lead us to believe that the drug, by reducing the number of bacteria, also indirectly reduces the amount of toxin produced. Penicillin undoubtedly reduces the fever duration, as shown in table XII and XIII. However, the institution of early treatment is of equal importance, as shown in table IX. Early vigorous penicillin treatment subdues the bacterial invasion and indirectly reduces the amount of toxin produced. The general inflammatorial reaction is less, and the fever duration is decreased.

In the literature of the last 10 years there are no wide disagreements of opinion in regard to this action of penicillin on the fever of scarlet fever. Most workers agree that penicillin is beneficial.

The reports from the United States in early 1947, like those of Hoyne and Brown, were limited in their enthusiasm for penicillin. Stambach and Larcher, 1948, in a series comparing cases treated with penicillin and cases treated symptomatically, reported that the latter group did as well as the treated group as regards fever duration. The explanation for these adverse comments is undoubtedly the low dosage of penicillin that these workers used. In U.S.A. Hirsh, Dowling and Sweet (1947), in a series of 86 patients treated with

dosages of 200 000 U. penicillin daily for 5 days, noted a 3 days reduction in the fever duration between these 68 patients and previously untreated cases.

Danish authors, like Jersild (1948), and Norwegian authors, like Ancherson (1947), also reported temperature reduction with treatment.

In Switzerland, from Geneva, Rilliet, Gautier, Guinand and Thélin also indicated that the fever duration was diminished with penicillin treatment.

In Basel, Zürcher, in the large epidemic of 1948, also used 200 000 to 300 000 U. daily for 5 days and reported that the fever was shortened.

In Germany the importance of the early commencement of treatment was studied. Schmeiser and Mattheck, Friederiszik, Ambrust and Blum, and Buss, all stressed that the efficacy of penicillin against the fever was enhanced when the treatment was begun promptly. Also in Germany Klaus Ebert, in an epidemic in Wolfsburg in the winter of 1950—1951, observed 274 cases. He divided his case material in a manner very similar to our case material. Some patients received no penicillin, others $8 \times 12\,000$ U. daily, and still others 200 000 to 800 000 U. daily, depending on the severity. They noted also a decrease in the fever duration which was all the better the higher the dosage. Their patients were on the average 2 to 3 days ill at home and they reported the fever duration, after admission to the hospital. The results were 4.13, 2.9 and 2.4 days of fever, decreasing inversely as the penicillin dosage was increased.

In the U.S.A. Mathieu and West (1951), in a series with 386 patients, also were impressed with penicillin's effect on the fever.

In the Geneva epidemic in 1948, Rilliet at the University Clinic, observed 24 adults and 135 children and noted a distinct drop in temperature duration, as antibiotics were administered.

In our group III, patients during 1954, 1955 and 1956, we noted, as shown in table X and XI, an average fever duration of 3.35 days, and in those patients that had received penicillin in their first 2 days of sickness, a further reduction to an average of 2.7 days. These tables show that the fever is most influenced when the penicillin dosage is maximal, and that to achieve the ultimate in results, this maximal dosage should be administered as promptly as possible. It is

apparent, as we regard the curves of groups I, II, II x, III and III x, that the dosage as well as the rapid commencement of treatment is important. Which is more important is difficult to say. As dosage is increased, the fever period is shortened. With the early institution of therapy, the fever period is also shortened. The maximum benefit is reached when both are combined.

Maué and Sinios (1950), in the medical department at the Heidelberg Hospital in Hamburg-Langenhau, were especially interested in this aspect of the treatment. They had a case material of 439 patients of which 165 were treated symptomatically and of which 274 were treated with penicillin. Children up to 5 years received 180 000 U. daily for 6 days; children up to 14 years received 240 000 U. daily for 6 days and adults 300 000 U. daily for 6 days. It was noted that the 8 day fever average of untreated patients was reduced to 5 days by treatment and to only 3 days by early treatment.

In table XII is presented a composite graph of our 2286 patients, representing graphically the antipyretic action of penicillin. As penicillin is administered in high enough dosage, the bacteria are killed and the fever reduced. As penicillin treatment is instituted early, the bacteria are killed quicker and less toxin is produced, and this indirectly also reduces the fever.

Table X
Group III

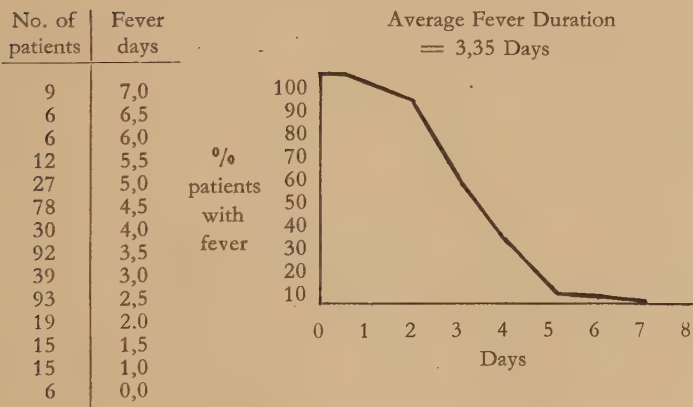


Table XI

Group III x

No. of patients	Fever days
6	4,5
6	4,0
51	3,5
30	3,0
75	2,5
15	2,0
10	1,5
12	1,0

Average Fever Duration
= 2,7 Days

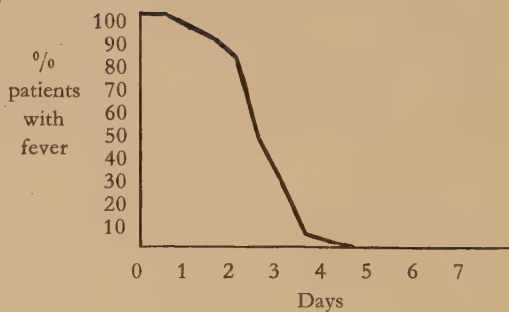
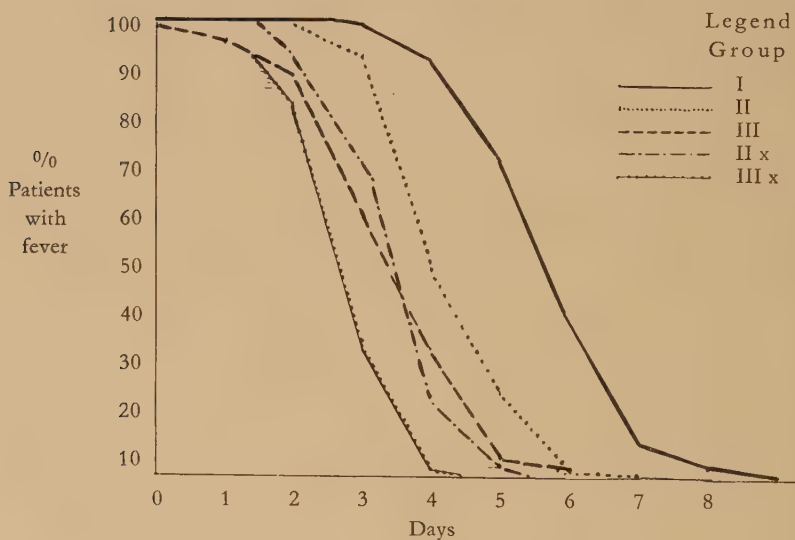


Table XII

Composite Fever Graph



Analysis of Exanthema

The exanthema is an integral part of the initial toxic manifestations and is caused by the erythrogenic toxin which is produced by

the streptococcus. It is taken for granted that penicillin cannot destroy or neutralize the toxin. The only method by which penicillin can work, is by destroying the bacteria and thereby reducing the amount of toxin created.

Reports on the effect of penicillin treatment on the exanthema of scarlet fever are quite controversial. Hoyne and Brown (1948), in Chicago, observed the exanthema in their 116 cases. As noted above, their comments about the action of penicillin on the fever were unfavourable. In contrast, the exanthema duration, even with such small amounts of penicillin as 80 000 U. daily for 5 days, was found to be shortened. In the penicillin treated cases, the average was 2.93 days, while in the untreated cases it was 3.44 days. They used as their criteria exanthema duration after hospital admission. In France, Justin-Besançon, Klotz and Luguët, observed a shorter exanthema duration, using 200 000 U. daily. In Germany, Schmeiser (1952), Friederiszik (1950), and Hangartner and Siebert (1951), were all impressed by the results and reported, among other things, that the exanthema was reduced both in intensity and in duration.

Scandinavian literature, especially that of Jersild, is mostly unfavourable. Various German workers were not impressed. Among these were Mayer of the University Clinic in Homburg, the Saar, who in 1953, commented negatively on the beneficial role of penicillin on the exanthema. Ströder (1953), also saw no benefit.

Our own results among our 2286 patients are analysed in tables XIII to XVIII.

One can see by comparing group I and II in tables XIII and XIV that there is statistically very little difference. However, of the 1419 patients in this latter group, 583 were treated on the first or second day of the illness and this group has an average exanthema duration of only 4.2 days with a curve as shown in table XV. The patients treated after the fourth day, have an average exanthema duration longer than 5 days. This indicates that, as a prerequisite for penicillin, to be effective against the exanthema, early treatment is necessary. When treatment is delayed, the exanthema is uninfluenced. On the next page are tables XIII, XIV and XV.

Table XIII

Group I

No. of patients	Exanthema days
-----------------	----------------

78	7
66	6
138	5
102	4
12	3
12	2
66	1
0	0

%
patients
with
exanthema

Average Exanthema Duration
= 5,0 Days

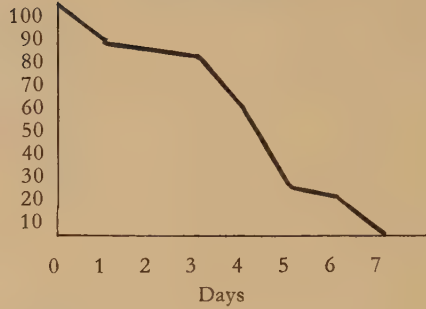


Table XIV

Group II

No. of patients	Exanthema days
-----------------	----------------

42	7
283	6
564	5
394	4
88	3
16	2
17	1
15	0

%
patients
with
exanthema

Average Exanthema Duration
= 4,74 Days

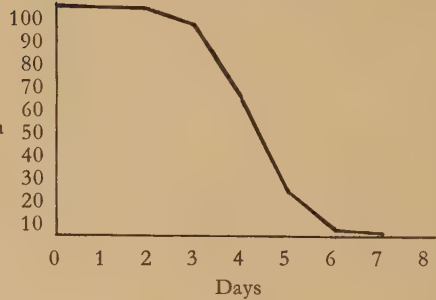


Table XV

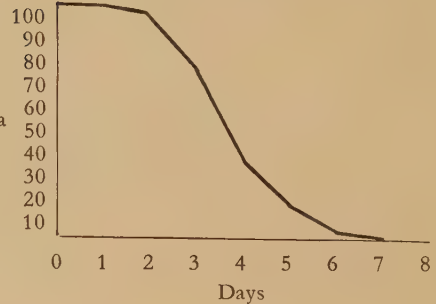
Group II x

No. of patients	Exanthema days
-----------------	----------------

19	7
72	6
161	5
172	4
131	3
21	2
0	1
7	0

%
patients
with
exanthema

Average Exanthema Duration
= 4,2 Days



The 447 patients from 1954, 1955 and 1956, making up group III, also received their first treatment on various days. Below in tables XVI and XVII this group is analysed.

Table XVI

Group III

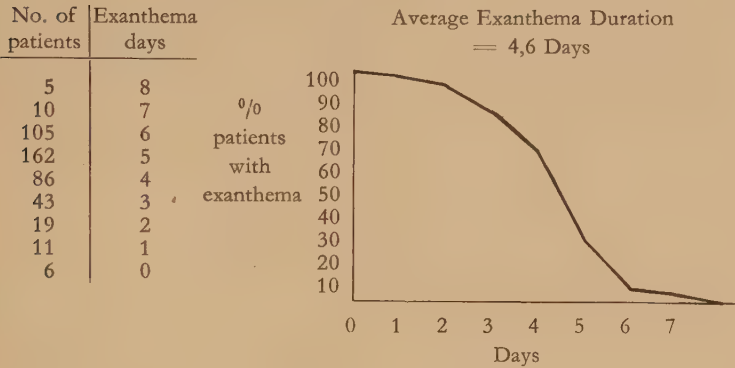
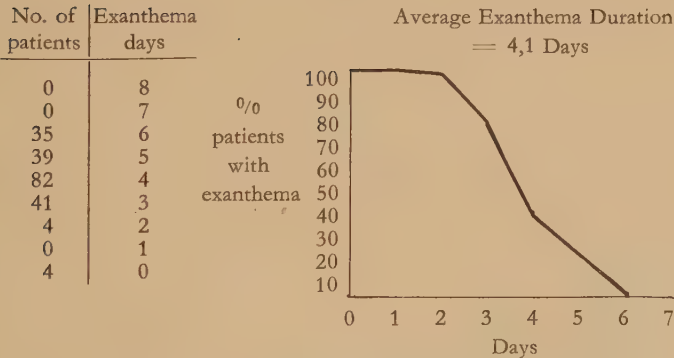


Table XVII

Group III x

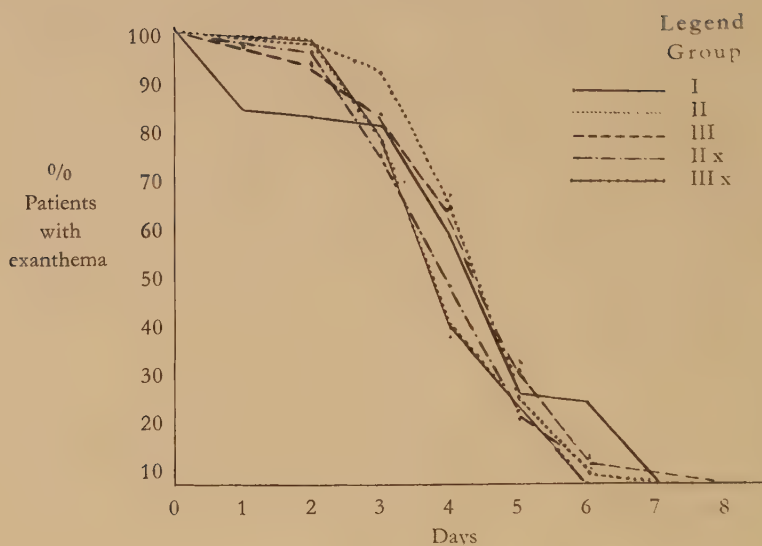


In all, they have an average exanthema duration of 4.6 days and an average of only 4.1 days in the patients treated on the first 2 days.

We can conclude from our figures that the effect of penicillin on the duration of the exanthema is slight and that, to achieve even this slight benefit, early treatment is imperative.

On page 22 is a composite graph of the exanthemas.

Table XVIII
Composite Exanthema Graph



Below, in tables XIX and XX can be seen graphically, how the fever is influenced more than the exanthema by the penicillin treatment.

Table XIX
Fever Averages

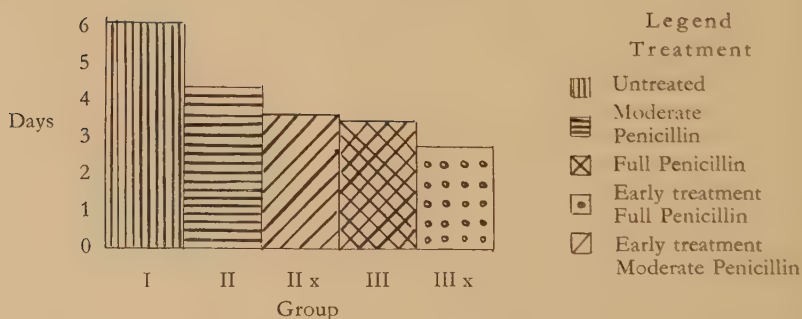
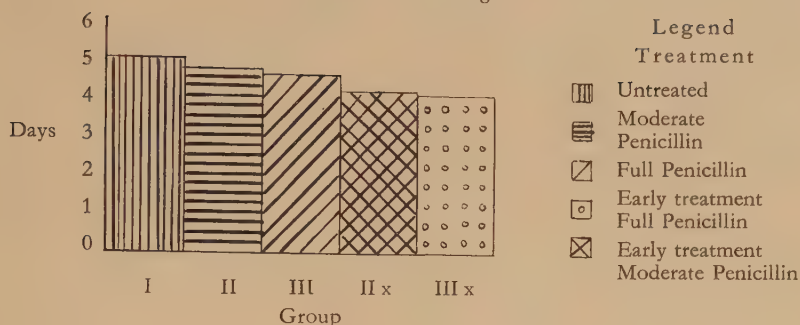


Table XX

Exanthema Averages



Analysis of Complications

Before we discuss the influence of penicillin on the complications, we would like to discuss a concept in this disease caused by its multiple etiology. Hottinger, Mayer and other authors have stressed for many years that the number of scarlet fever complications is dependent not only on the penicillin dosage and the duration of treatment, but also on proper hospital isolation. Hottinger has always insisted that the complications of patients treated with penicillin decreases, as the possibility of superinfection was eliminated by proper isolation in the hospital. Mayer (1953) indicated that patients treated with penicillin, and not protected from superinfection or reinfection, had an increased number of complications! These complications were not due to the original streptococcus which, with proper penicillin treatment, is eliminated in a few days, but were caused by other types of group A streptococcus introduced into the hospital ward mainly by new sick patients. The neglect of taking precautions to guard against this danger probably explains most of the negative results obtained in the late 1940's and early 1950's, when many authors reported more complications with treated patients than with control patients. These workers misjudged penicillin and attributed many complications to the ineffectiveness of penicillin that were, in point of fact, attributable to a superinfection occurring after antibiotic treatment had ended. Jersild (1948) considers 50 % of all complications and practically

100 % of all relapses as superinfections. Therefore Hottinger and other authors advise proper penicillin treatment, careful hospital isolation to prevent superinfection and hospitalization not longer than necessary. All of these must be combined. One without the other detracts from the endresult. In Basel all of these criteria were met, so that a fair judgment of the effect of penicillin on scarlet fever complications could be made.

The complications are divided into two types. The first type is caused mainly by direct bacterial invasion and includes lymphadenitis, otitis media, rhinitis, pharyngitis, pyoderma, stomatitis, paronychia, pneumonia, relapse, secondary angina, conjunctivitis, sepsis and secondary exanthema. Relapse is included, although in the vast majority of the cases it is a superinfection.

The second type of complication is the allergic-toxic complication and includes heart complications like myocarditis, nephritis, hepatitis, rheumatoid, erythema nodosum and purpura. The second type, the non-suppurative complications, the "zweite Kranksein" in the German literature, are the late complications of scarlet fever and streptococcal infections in general. Streptococcal infections and scarlet fever are characterized by an acute toxic and septic phase which usually lasts one week. Suppurative complications may occur at any time after the onset of the disease until the third or fourth week. Following the acute stage, the patient seemingly recovers completely, and for a period ranging from a few days to 6 or 8 weeks no symptoms appear. Then appear the so-called allergic toxic symptoms like glomerulonephritis, erythema nodosum, erythema multiforme and rheumatoid. These usually appear during the third week of the illness. Often, especially in the Anglo-Saxon literature, a clinical unit is described, called rheumatic fever. It consists of any combination of these allergic-toxic complications such as polyarthritis, endocarditis, myocarditis and pericarditis. The mechanism of these allergic-toxic complications is unknown. Schick, in 1907, suggested an altered sensitivity to certain products of the streptococcus. Others speak of an antigen-antibody reaction.

Literature concerning penicillin's action on the complications are contradictory but not confusing. It is caused by various factors like different definitions of the complications, disregard of precautions against superinfection, and variation in the dosage. Ströder and

Erbig (1951) in the University Clinic in Würzburg, Germany, consider penicillin detrimental. Between autumn 1948 and spring 1950 they compared 100 patients treated with penicillin and 100 control patients and found 38 % complications with penicillin and 37 % in the control group, with more nephritis in the control group. Herrlich (1949) treated 252 patients: 123 with 200 000 U. penicillin daily for 6 days and 129 treated symptomatically and found 114 % complications with penicillin and 78 % without. Another negative report was from Stambach and Larcher (1948), comparing 50 penicillin treated patients with 50 control patients and finding 23 % complications with penicillin and 8 % without.

On the other hand, some of the more favourable reports were those of Jersild, who treated 1000 patients and found 49 % complications in the control patients decreasing to 5 % with penicillin treatment, and Ancherson (1947) with complications dropping from 54 % to 29 % as a result of penicillin treatment. Gautier in Geneva, with 74 patients, 40 without and 34 with penicillin, noted a drop from 67,5 % to 14,7 % with the antibiotic treatment. Also many reports stressed the increased efficacy achieved with higher dosage and increased time of treatment. Wiesner (1953) probably reports the best results with penicillin. He achieved the amazingly low complication rate of 1,1 % by combining proper penicillin treatment, complete isolation and quick hospital discharge. From Eastern Europe, especially Czechoslovakia, Prochozka (1949) and Kredba (1949), with a 6 day penicillin treatment, complete isolation, and quick discharge have achieved a 0,5 % complication rate.

We will now present our results from Basel. As in the fever and exanthema we have divided our 2286 patients into group I, II and III and subdivided groups II and III into three subgroups, according to the day in which penicillin treatment was started. In table XXI are our results:

Table XXI

Number of Complications				Percentage of Complications		
Group	I	II	III	I	II	III
No. of patients	420	1419	447			
Complications				%	%	%
Lymphadenitis	51	79	5	12,14	5,50	1,12
Otitis Media	43	30	27	10,23	2,10	6,04
Rhinitis	31	35	7	7,38	2,45	1,56
Pharyngitis	25	36	5	5,97	2,52	1,12
Pyodermia	29	11	7	6,80	0,72	1,56
Second. Exanthema	9	6	0	2,14	0,42	0,00
Stomatitis	9	6	3	2,14	0,42	0,67
Panaritium	14	10	2	4,11	0,70	0,45
Relapse	10	11	8	2,35	0,72	1,79
Pneum. + Grippe	9	14	4	2,14	0,97	0,89
Angina Secondary	9	32	6	2,14	2,10	1,34
Pyrexia Secondary	4	8	1	0,95	0,55	0,22
Conjunctivitis	5	5	1	1,09	0,35	0,22
Sepsis	0	1	0	0,00	0,07	0,00
Nephritis	4	6	2	0,95	0,42	0,45
Heart	4	5	4	0,95	0,35	0,89
Rheumatoid	2	2	0	0,47	0,14	0,00
Hepatitis	1	1	0	0,25	0,07	0,00
Erythema Nod.	1	0	0	0,25	0,00	0,00
Purpura	2	0	0	0,47	0,00	0,00
Total	262	298	82	62,92	20,57	18,32

Distribution of Complications according to Group

The complications in group I amounted to 62,9 % and most were of the suppurative type. Lymphadenitis was the most frequent, being 12,1 % while otitis media was second most frequent, being 10,1 %. Rhinitis, pharyngitis and pyodermia were the next most frequent.

In group II there is a sharp reduction of complications to 20,5 % with all the complications sharing in the reduction. There is a further decrease of 3 % in group III. The toxic-allergic complications are also reduced proportionally from an average of 4,1 % in group I to an average of 1,1 % in group II and III.

Lymphadenitis is the complication most sharply reduced — from 12,14 % to 1,1 %. This is an excellent result, and most other clinicians report their final figures higher than ours. On the other hand, some show a larger total amount of reduction. Hoen and Kaiser report a reduction from 40 % lymphadenitis in control cases to 9,1 % in treated cases. Similarly, Schmeiser (1950) noted a reduction from 18,1 % in untreated cases to 3,5 % with antibiotic therapy.

The otitis media figures are difficult to explain. The reduction from 10,3 % in group I to 2,1 % in group II is encouraging. Then in group III there is a rise to 6,04 %. One case in group II developed sinusitis, and one case mastoiditis, while in group I these did not appear. The literature is replete with more favourable results than ours. Among these can be mentioned Friederiszik (1950), Hoen and Kaiser (1949), Jersild (1948), and Förster and Leopold (1953). The last two achieved the ultimate in results with otitis media completely eliminated with penicillin treatment. Certainly the rise of the number of otitis media complications in group III should not speak against the effectiveness of penicillin. It is at complete variance with the other complications, which are reduced. The probable explanation is the inclusion of a large number of slight inflammatory condition of the tympanic membrane and abortive cases that previously were not considered sufficiently significant to be called complications.

Rhinitis, pharyngitis and secondary angina are also reduced. The low final figures, averaging 1,5 %, are to be expected as these are pure bacterial complications. In group II one case of sepsis was seen, a rarity with penicillin.

Relapses have also declined in number, but strangely group III shows a higher average than group II. Hottinger, Banks, Wiesner, Maué and other authors consider relapses as superinfections. Maué has reduced relapses from 15 % in control cases to 0,4 % in treated cases by avoiding superinfections. Not all reports on relapses are favourable. Sauerbrei (1950) noted an increase in relapses to 12,5 % by treatment as contrasted to the 4,6 % in control cases. Herrlich had a mere 1,5 % relapse average in his control cases. When he began to treat his patients with penicillin, the percentage increased to 5,7 %. Both of these discouraging reports are probably caused by superinfection and should not speak against penicillin therapy.

In addition to the suppurative complications, the allergic-toxic

complications also are sharply reduced by more than 200 %. The exception is the heart complication group which remains the same. Nephritis is reduced in half and rheumatoid in group III is completely eliminated. So of the three major constituents of the allergic-toxic type, it would appear from our results that rheumatoid is the one most significantly influenced. Nephritis, also, is considerably influenced. Of the minor constituents, all seem equally benefited, and in group III hepatitis, erythema nodosum and purpura have completely disappeared. It must be admitted that the total number of complications of this type in both the control and treated groups are few in number, and it is difficult to draw conclusions from this limited material, but the difference is still apparent and in favour of the penicillin therapy.

The variation in the incidence of nephritis has been attributed by Rammelkampf and Weaver (1953) to variations in the type of streptococcus, with type 4 and 12 most nephrotoxic. Others have had more spectacular results in the reduction of the kidney complications with larger amounts of material, for example, Hoen and Kaiser, in control cases: nephritis 9,1 % reduced to 1,8 % with penicillin treatment. Förster and Leopold (1953) were discouraged with penicillin, noting a rise from 7,2 % without treatment to 8,6 % with treatment. Schmeiser analysed 1228 control cases and found 1,96 % nephritis, while in 3356 cases treated with penicillin, nephritis was a mere 0,36 %. The ultimate was reached in 1948 by Jersild with not a single kidney complication in 2000 penicillin treated cases. In Zürich, Girardet, Romm and Zellweger (1950) had with 350 penicillin treated cases one nephritis; and similarly, Grünberg (1951) in 720 penicillin treated cases only one nephritis. Hottinger (1953) says that nephritis has been very favourably influenced by the use of penicillin. In conclusion, nephritis is, according to our material and the current literature, very much reduced by vigorous penicillin treatment.

Of the major allergic-toxic complications of scarlet fever, rheumatoid causes the most confusion. This confusion stems directly from the varied use of the word rheumatoid. This confusion in terminology is due to the fact that rheumatoid symptoms can appear at any time during the illness and can have a varied pathogenicity (Glanzmann). The cause can be toxic, bacterial or allergic-toxic. In

addition, superinfection can complicate the situation still further. Many authors use the term rheumatoid synonymously with acute polyarthritis, the more severe joint complication often coming later in the illness. The Anglo-Saxon literature has added more confusion by using an all inclusive term "Rheumatic Fever", a clinical combination of any of the following: polyarthritis, endocarditis, pericarditis and chorea.

In our study and in our usage rheumatoid is distinguished and used separately from acute polyarthritis. When one uses the term rheumatoid in our meaning, the literature is understandable. As noted previously, Hottinger was one of the first authors to insist that the rheumatoid complication of scarlet fever was insignificantly influenced by penicillin treatment. Herrlich's report in 1949 showed more rheumatoid after penicillin treatment (9,8 %) than previously in untreated cases (7,7 %). Sauerbrei (1950) also insisted that the rheumatoid remains the same after treatment. Most authors agree that the rheumatoid is not benefited.

In contrast, the acute polyarthritis seems definitely benefited by penicillin treatment. Rammelkamp (1952), Breeze (1955). Since this complication is so often associated with heart complications, it will be more fully discussed later.

Our heart complications show a decline of 150 % from group I to group II. In group III there is an increase. When one surveys the literature about this complication, one summarizes that it is much more frequent and dangerous than thought. Contradictions in the literature about this complication are caused by the use of different methods of diagnosis and study. Hellwich and Hellwich (1951), in Dresden, showed 73 % electrocardiographic changes in 100 scarlet fever patients, treated with penicillin, with very few of these patients showing physical signs of heart involvement. Steinmann, in Switzerland (1945), also indicates that physical examination will not reveal these complications. This explains the divergent results concerning penicillin treatment on this complication — one group uses serially made ECG studies and another group uses only physical diagnosis. Are these complications more frequent than we think? Before a critical analysis of the influence of penicillin on this complication can be made, standardized criteria, substantiated by electrocardiographic studies must be made. Where this has been made,

the consensus of opinion is that penicillin treatment considerably helps. Acute antibiotic treatment of all streptococcal diseases, including scarlet fever, is generally considered a means of prophylaxis against heart complications. Rammelkampf (1952), Rantz (1952), Hauser and Eckhardt (1952), Breeze and Disney (1955). In the U.S.A., where the term rheumatic fever is used to include the heart complications, one study showed that penicillin reduced rheumatic fever by over 95 % (Wannamaker and Rammelkampf, 1951).

Table XXII shows how the early commencement of treatment influences the efficacy of the penicillin treatment. Patients receiving

Table XXII

Number of Complications				Percentage of Complications		
Treatment Begin	1 st & 2 nd day	3 rd & 4 th day	5 th day & over	1 st & 2 nd day	3 rd & 4 th day	5 th day & over
No. of patients	788	934	144			
Complications				%	%	%
Lymphadenitis	29	46	9	3,60	4,90	6,25
Otitis Media	23	29	5	2,80	3,10	3,50
Rhinitis	15	20	7	1,90	2,10	4,90
Pharyngitis	15	22	4	1,90	2,30	2,80
Pyodermia	6	10	2	0,76	1,06	1,40
Second. Exanthema	2	3	1	0,25	0,32	1,70
Stomatitis	2	5	2	0,25	0,53	1,40
Panaritium	3	7	2	0,53	0,74	1,40
Relapse	6	10	3	0,76	1,06	2,10
Pneumonia	6	9	3	0,76	0,96	2,10
Angina Secondary	12	19	7	1,50	2,01	4,90
Pyrexia Secondary	3	5	1	0,53	0,53	0,90
Conjunctivitis	2	3	1	0,25	0,32	0,70
Sepsis	0	1	0	0,00	0,11	0,00
Nephritis	2	4	2	0,35	0,42	1,40
Heart	1	6	2	0,18	0,63	1,40
Rheumatoid	0	2	0	0,00	0,21	0,00
Hepatitis	0	1	0	0,00	0,11	0,00
Total	127	202	51	16,32	21,42	36,85

Distribution of Complications according to Beginning of Therapy

penicillin on the first two days of their illness, had 16,3 % complications. When commencement of treatment was delayed, complications increased 5 % to 21,4 %. They were more than doubled by further delay, reaching a figure of 36,8 % in the patients treated very late. All this is shown in table XXII.

We have already mentioned Rilliet and Kraft who especially emphasized the early beginning of treatment to reduce fever. They also showed how early commencement of treatment benefits both the bacterial and the toxic-allergic complications. In our case material both are also proportionally reduced.

An interesting study was made also to see the distribution of multiple complications. In each group the number of patients was determined with no complications, with one complication, with two complications, and so on.

Below, in table XXIII, one sees the actual number of each, and in table XXIV these figures are calculated into percentages.

Table XXIII

		Number of Complications pro Patient					
		0	1	2	3	4	5
Number	Group I	229	135	42	13	1	0
of	Group II	1157	231	26	5	0	0
Patients	Group III	379	55	12	1	0	0

Distribution of Multiple Complications

One sees that the number of patients in group II and III with no complications is over 80 %, while in group I only 50 % of the patients are complication free. This means that, previous to antibiotic treatment, one out of each two patients developped a complication. In group I patients with 2 and 3 complications exceed these in group II and III, and the only patient with 4 complications is in group I. Not one case in 10 years had 5 or more complications.

Table XXIV

		Complications					
		0	1	2	3	4	5
%	Group I	54,0 %	32,6 %	10,0 %	3,1 %	0,3 %	0,0 %
of	Group II	81,4 %	16,3 %	1,7 %	0,5 %	0,0 %	0,0 %
Patients	Group III	84,7 %	12,3 %	2,7 %	0,3 %	0,0 %	0,0 %

Distribution of Multiple Complications

Table XXV

Number of Complications				% of Complications		
Age Group	0—4	5—8	over 8	0—4	5—8	over 8
No. of patients	604	898	364	32,4 %	48,2 %	19,4 %
Complications				%	%	%
Lymphadenitis	24	43	17	4,10	4,90	4,60
Otitis Media	18	26	13	3,00	2,70	3,43
Rhinitis	17	18	7	2,83	2,00	1,80
Pharyngitis	13	24	4	2,16	2,60	1,10
Pyodermia	3	9	6	0,50	1,00	1,60
Second. Exanthema	2	3	1	0,33	0,33	0,23
Stomatitis	3	4	2	0,50	0,44	0,55
Panaritium	1	6	5	0,16	0,66	1,37
Relapse	3	11	5	0,50	1,40	1,37
Pneumonia	3	11	4	0,50	1,40	1,10
Angina Secondary	12	20	6	2,00	2,20	1,60
Pyrexia Secondary	4	3	2	0,66	0,33	0,55
Conjunctivitis	1	4	1	0,17	0,44	0,23
Sepsis	0	1	0	0,00	0,11	0,00
Allergic-Toxic	7	9	4	1,10	1,00	1,10
Total	111	192	77	18,51	21,51	20,63

Distribution of Complications according to Age

To test the relationship between age, penicillin and complications, group II and III were divided into 3 age groups and the various complications were distributed between the three age groups. In table XXV we see this.

As penicillin dosage is determined by age, this would indicate whether therapy was good. The age groups were 0—4, 5—8 and over 8. Most patients came in the middle group, 48,2 %, 19,4 % were older and 32,4 % younger. Although slight variations exist in the distribution of the complications in the three age groups, statistically these are insignificant.

In summary, one can say that penicillin decreases all complications both quantitatively and qualitatively. The decrease is dependent on large enough dosage and early treatment.

Hospitalization

Finally we considered how the hospital had benefited by the penicillin treatment. The hospital stay of each patient in groups I, II and III was calculated and the totals were averaged. The average for group I was 38,2 days, with several patients being hospitalized longer than 60 days. With penicillin treatment this average was sharply reduced. During the epidemic in Basel in 1948, many patients were discharged in 10 and 12 days. This was an emergency measure and was not made common practice after the epidemic. However, already in late 1948, it was common place to discharge a patient in 28 days. In the following years, this was reduced to 21 days. The average hospital stay of patients in group II was 23 days. The average for group III is 21 days, which is similar to other countries in Europe with comparable health regulations. In various countries a one week hospital stay of all patients has been advocated. This presumably reduces the danger of superinfection and therefore reduces the number of complications.

Irrespective of the purely medical benefits, the individual, the community and the hospital have all benefited economically and socially by this shortened hospital stay.

Side Reactions

Several problems have arisen with penicillin treatment, but they were not serious. For instance there were 12 cases of urticaria in groups II and III, all of which quickly recovered. Several cases of penicillin exanthema occurred usually after treatment had ended. Primary sensitivity to penicillin was encountered occasionally, which necessitated changing to another antibiotic. It is to be noted that in group I, the group without penicillin treatment, side reactions also occurred, such as serum sickness with serum treatment and toxic reactions with sulfonamide.

Perhaps one of the questions, which belong in this chapter, is the loss of immunity. Many accusations have been made that penicillin treatment has reduced the immunity of treated patients and that second attacks are now more frequent. We did not systematically study the problem. Serological tests such as anti-streptolysin titre determination were not regularly made to see if these were lower in treated patients than in control patients.

The Dick Test was not systematically made on treated patients, so our only method of judging this problem was clinically. In these 10 years, 9 patients presented themselves with second attacks. 2 patients presented themselves with third attacks. What is important is that the previous attack was never verified. It was very difficult to say whether the so-called first attack was really scarlet fever. What we can say with certainty is that the frequency of second attacks was more or less the same after the beginning of penicillin therapy as before it.

Summary

In relation to the scarlet fever cases in the Basel Children's Hospital in the years 1947—1956 the difference in the clinical course of the disease and the difference in the frequency and severity of complications is analysed, with and without penicillin therapy.

In the first chapter the etiology, the pathogenecity and the current definition of scarlet fever is given, and the relationship of scarlet fever to other streptococcal infections is discussed. In a short historical summary the superiority of penicillin therapy over earlier therapy methods, as e.g. sulfonamide, gamma-globulin and others, is considered. Through the action of penicillin on the haemolytic streptococcus, the toxin building capacity of the streptococcus is reduced, and therefore serum therapy is in most cases superfluous.

In the second chapter the case material is analysed and divided into three groups: 1) without penicillin therapy, 2) penicillin in moderate amounts, chiefly penicillin per os, and 3) penicillin therapy with full dosage. To correctly consider penicillin therapy, it is necessary to separate the cases in which penicillin therapy was started early from those in which therapy was started later.

The duration and severity of the fever (3rd chapter) is definitely reduced with penicillin therapy.

The scarlet fever exanthema is considerably reduced with penicillin (chapter 4) in severity and intensity.

In the fifth chapter the influence of penicillin on the complications is considered. Significantly reduced are the bacterial or septic complications. Less reduced, as is to be expected, is the influence of penicillin on the toxic-allergic complications.

The role of superinfection by other streptococcus types is repeatedly indicated.

In the sixth chapter are mentioned the psychological and social benefits accruing from a reduced hospital stay which is made possible by penicillin therapy, and in the seventh chapter are mentioned the relative rarity and insignificance of penicillin side reactions.

Penicillin therapy for scarlet fever is in our opinion the treatment of choice, and it gives all the better results, the quicker therapy is instituted.

Zusammenfassung

Anhand der Scharlachfälle des Basler Kinderspitals in den Jahren 1947—1956 wird der Unterschied im Verlauf des Scharlachs und der Häufigkeit und Schwere der Komplikationen ohne und mit Penicillintherapie analysiert.

Im ersten Kapitel wird die heute gültige Definition des Scharlachs und seiner Aetiologie und Pathogenese gegeben, und die Beziehungen des Scharlachs zu anderen Streptokokkenerkrankungen diskutiert. In einem kurzen geschichtlichen Ueberblick wird die Ueberlegenheit der Penicillinbehandlung über andere frühere Behandlungsmethoden wie z. B. mit Sulfonamiden, Gamma-Globulinen u. a. belegt. Durch die Wirkung des Penicillins auf die hämolytischen Streptokokken wird auch die Toxinbildung der Streptokokken eingeschränkt und dadurch in vielen Fällen die Serumbehandlung überflüssig gemacht.

Im zweiten Kapitel wird das Krankengut analysiert und in die 3 Gruppen eingeteilt: 1. ohne Penicillinbehandlung, 2. Penicillin in niedriger Dosierung (hauptsächlich Penicillin per os), 3. Penicillinbehandlung mit voller Dosierung. Zur richtigen Beurteilung der Penicillintherapie war es notwendig, die frühzeitig behandelten Fälle von denjenigen abzutrennen, die erst am 3. Krankheitstag oder noch später Penicillin erhielten.

Dauer und Höhe des Fiebers (3. Kapitel) sind durch Penicillin deutlich herabgesetzt.

Das Scharlachexanthem wird durch Penicillin an Stärke und Dauer ebenfalls eindeutig reduziert (Kapitel 4).

Im 5. Kapitel wird ausführlich die Frage der Beeinflussung der Komplikationen des Scharlachs behandelt. Eindeutig ist die Häufigkeit der bakteriellen bzw. septischen Komplikationen durch Penicillin herabgesetzt. Weniger eindeutig, wie es zu erwarten war, ist der Einfluß des Penicillins auf die toxisch-allergischen Komplikationen.

Wiederholt wird die bedeutende Rolle der Superinfektion mit anderen Streptokokkentypen betont.

Im 6. Kapitel wird noch kurz auf die psychologisch und sozial günstigen Auswirkungen der Verkürzung des Spitalaufenthaltes durch Penicillin hingewiesen, und im 7. Kapitel auf die relative Seltenheit und Leichtigkeit der Nebenerscheinungen der Penicillintherapie.

Die Penicillintherapie des Scharlachs ist auch nach unserer Auffassung die Methode der Wahl, und sie gibt umso bessere Resultate, je früher sie begonnen wird.

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